REMARKS

This Request for Continued Examination (RCE) is in response to the final Office Action mailed July 29, 2004. Claims 1 to 4, 6 to 8, 10, 12 to 21, 23 to 25, 28 and 29 to 40 are pending. Claim 30 has been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claim in any related application claiming the benefit of priority of the subject application. Accordingly, upon entry of the RCE, claims 1 to 4, 6 to 10, 12 to 21, 23 to 25, 28, 29 and 31 to 40 are under consideration.

Regarding the Claim Amendments

The amendments to claims 1, 12, 13 and 14 are supported throughout the specification. Support for the recitation of "wherein said mammal (or human) has a genetic defect which can result in generation of inhibitory antibodies to a protein (or a blood coagulation protein)," can be found for example, at page 11, lines 1-7, which discloses that the invention provides a solution to inhibitor formation directed to the gene therapy based delivered protein, even when the genetic defect being corrected is most likely to result in the generation of inhibitory antibodies against the delivered protein. Thus, as the claims amendments are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

I. CLAIM OBJECTIONS

The Examiner indicates that claims 1, 6, 8, 12 to 14, 17, 18 and 25 do not comply with 37 C.F.R. §1.121 due to the use of a status identifier. Claim 30 is also indicated to be a substantial duplicate of claim 33.

Applicants appreciate that the Examiner has provided Applicants with the opportunity to provide claims status identifiers in accordance with 37 C.F.R. §1.121. As set forth above, the claim status identifiers comply with 37 C.F.R. §1.121. In addition, claim 30 has been cancelled herein without prejudice. Accordingly, Applicants respectfully request that the objection to the claims be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §103(a)

Wilson et al., Bach and Tripathy et al.

The rejection of claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35, 37, 38 and 40 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) in further view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is respectfully traversed. The grounds for rejection are as in the record.

The claims prior to and following entry of the RCE would not have been obvious in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in combination. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth herein. Although the following remarks are directed to the claims as amended herein, they are also applicable to the claims prior to the amendments of the RCE.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must be 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) the combination of references must teach or suggest each and every element of the claimed invention; and 3) a reasonable expectation of success at the time of the invention. Both the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success *must both be found in the prior art, not in Applicants' disclosure.* See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988), *Emphasis added.* "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art *suggested the desirability of the modification.*" *In re Gordon,* 733 F.2d 900, 902 (Fed. Cir. 1984); *See, also, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990), *Emphasis added.* Furthermore, the prior art must be considered in its entirety....including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Here, *inter alia*, there would not have been a motivation to combine or modify the cited references in order to produce the claimed methods, nor a reasonable expectation of success of producing the claimed methods, in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, at the time of the invention. Moreover, Tripathy *et al.* and Herzog *et al.* (Blood 90, part 1, Supp. 1, abstract 1057 (1997)) each teach away from producing the claimed methods.

First, with respect to the alleged inability to use Herzog *et al.* (Blood 90, part 1, Supp. 1, abstract 1057 (1997); hereinafter referred to as "Herzog Blood") as evidence of a teaching away from the claimed methods, Applicants respectfully point out that the courts have never made a distinction between cited and uncited art in considering obviousness under 35 U.S.C. §103(a). The Federal Circuit has repeatedly stated that all evidence bearing on the issue of obviousness must be considered. For example, in *Gore*: "All evidence bearing on the issue of obviousness, as with any other issue raised in the conduct of the judicial process, must be considered and evaluated *before* the required legal conclusion is reached." *Id.* at 1550. In *Stratoflex*: "It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included." *Stratoflex, Inc. v. Aeroquip Corporation*, 713 F2d 1530 (Fed. Cir. 1983). Thus, the Patent Office must consider all objective evidence of non-obviousness, whether the evidence is a reference cited by the Patent Office or not. Thus, Herzog Blood which teaches away from producing the claimed methods, must be considered by the Patent Office.

The claims under consideration are directed to methods of preventing or reducing formation of an inhibitory antibody to a blood coagulation protein or a protein delivered to a mammal or human by way of gene therapy. The amended claims require that the mammal or human has a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Claims 1 to 4, 6 to 8, 10 and 20 require, *inter alia*, that cyclophosphamide or anti-CD40 ligand, be administered prior to or simultaneously with the gene therapy before formation of said inhibitory antibodies. The claimed methods also require, *inter alia*, delivery of a blood coagulation protein which is the "same species" as the mammal to which it is delivered. Claims 12 to 21, 23 to 25, 29 and 31 to 40 require administering an immunosuppressive agent prior to or simultaneously with gene therapy before formation of inhibitory antibodies, the delivered protein being the same species as the mammal (or human protein delivered to a human, claim 14).

As pointed out in the record, Wilson *et al.* describe recombinant adenovirus expressing human placental ALP gene, and infecting mice administered either antibody to CD4+ cells, Il-12 or gamma interferon with this recombinant adenovirus. Mice treated with antibody to CD4+ cells, Il-12 or gamma interferon exhibited higher levels of human ALP expression than controls. Wilson *et al.* also report infecting mice with a recombinant adenovirus expressing human LDL receptor gene. However, in contrast to the claimed methods, in every case, the genes introduced

into mice were human. Furthermore, Wilson *et al.* expressly state that the purpose of the method is to reduce immune response against a viral gene therapy vector (see, for example, abstract; column 2, lines 36-44; column 4, lines 35-39; and column 6, lines 16-19). Nowhere do Wilson *et al.* teach or suggest delivering a protein to a mammal or human by way of gene therapy where the protein is the same species as the mammal to which it is delivered, let alone a blood coagulation protein that is the same species as the mammal to which it is delivered. Furthermore, nowhere do Wilson *et al.* teach or suggest delivering a protein to a mammal or human by way of gene therapy where the mammal or human has a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein.

Bach (WO 96/25177, U.S. counterpart Patent Publication No. 2003/0004091) report delivering an adenovirus expressing bacterial gene along with an immunoprotective gene into mice. As pointed out in the record, Bach is identical to Wilson *et al.* in that the delivered gene (bacteria) is a different species than the animal to which it is delivered (mouse). Nowhere does Bach teach or suggest delivering a protein by way of gene therapy where the protein is the same species as the mammal to which it is delivered, let alone a blood coagulation protein that is the same species as the mammal to which it is delivered. Furthermore, nowhere do Bach teach or suggest delivering a protein to a mammal or human by way of gene therapy where the mammal or human has a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Thus, the combination of Wilson *et al.* and Bach fail to teach or suggest the claimed methods.

Furthermore, neither Wilson *et al.* nor Bach teach or suggest that an immune response is produced against a protein that is the same species as the mammal to which it is delivered. In this regard, the Patent Office acknowledges that "Wilson teaches that an immune response can be the product of a transgene when that transgene expresses a protein that is foreign to the treated host." Thus, in view of the fact that the purpose of Wilson *et al.*'s method is to reduce the immune response against the foreign protein, it cannot objectively be argued that Wilson *et al.* would have motivated the skilled to administer an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, when the delivered protein is the same species as the mammal, at the time of the invention. Likewise, because the purpose of Bach's method is towards "preventing the rapid elimination of the adenoviruses from the infected cells," Bach neither teach nor suggest an immune response against a protein

delivered by way of gene therapy is produced, let alone inhibitory antibodies against a protein that is the same species as the mammal to which it is delivered. Absent such a teaching or suggestion, the skilled artisan would not have had any reason to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein, which is the same species as the mammal, prior to the mammal forming inhibitory antibodies against the blood coagulation protein or protein.

Moreover, neither Wilson *et al.* nor Bach mention that animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein can be employed, let alone teach or suggest using animals having such genetic defects in gene therapy protocols. Absent such a teaching or suggestion, the skilled artisan would not have had any reason to target animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein.

Tripathy *et al.* report studies of replication defective adenovirus gene therapy in mice in order to ascertain whether host immune responses were directed against viral proteins or against the transgene (see, for example, abstract and page 548). Based upon findings that mice injected with adenovirus harboring human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring murine EPO **did not** develop anti-EPO antibodies, Tripathy *et al.* conclude that "immune responses directed against foreign transgene-encoded proteins are the major determinants of the stability of gene expression following i.m. injection of RDAd." (see, for example, abstract; see, also, page 548, first and second columns).

As with Wilson *et al.* and Bach, Tripathy *et al.* fail to teach or suggest that an immune response is produced against a protein delivered by way of gene therapy when the protein is the same species as the mammal to which it is delivered. Consistent with this position, Tripathy *et al.* at most report that 1) administration of murine EPO to mice did not result in production of antibodies against mEPO; and 2) administration of human EPO to mice did result in production of antibodies against hEPO. Because the data in Tripathy *et al.* indicate that mice do not form inhibitory antibodies against murine EPO delivered by way of gene therapy, it cannot be objectively argued that Tripathy *et al.* teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a protein that is the same species as the mammal prior to the mammal forming inhibitory antibodies against the protein. Thus, the

combination of Wilson *et al.*, Bach and Tripathy *et al.* fail to teach or suggest each and every element of the claimed methods.

Moreover, given the fact that none of Wilson *et al.*, Bach, or Tripathy *et al.* teach or suggest that inhibitory antibodies are produced against proteins delivered by way of gene therapy to mammals, where the protein is the same species as the mammal to which it is delivered, the skilled artisan would not have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against the protein. In this regard, how can it objectively be argued that the skilled artisan would have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against a protein delivered by way of gene therapy, the delivered protein the same species as the mammal, when antibodies against the protein are not even formed in the absence of immunosuppressive agent?

As to the Office Action's statement at page 8, that "as stated by Applicants Tripathy teaches delivering a murine EPO gene to mice," Applicants respectfully point out that the claims, *inter alia*, require administration of an immunosuppressive agent prior to or simultaneously with delivery of protein by way of gene therapy, where the delivered protein *is the same species as the animal*. In this regard, in Tripathy *et al.*, mice administered the murine EPO transgene were <u>not</u> administered an immunosuppressive agent (see, for example, page 547, second column). The failure to teach or suggest administering an immunosuppressive agent to the mammal is because there is no logical reason to administer an immunosuppressive agent to prevent formation of inhibitory antibodies that are not even formed. In view of this deficiency, even if Wilson *et al.* and Bach, Tripathy *et al.* are combined, the combination fails to teach or suggest the claimed methods.

Finally, as with Wilson *et al.* and Bach, Tripathy *et al.* fail to mention using animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, let alone teach or suggest using animals having such genetic defects in gene therapy protocols. Absent such a teaching or suggestion, the skilled artisan would not have had any reason to target animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, as claimed. In view of this deficiency, even if Wilson *et al.* and Bach, Tripathy *et al.* are combined, the combination fails to teach or suggest the claimed methods.

Consequently, the cited Wilson *et al.*, Bach, and Tripathy *et al.* references are deficient for failing to meet two of the requirements for the rejection to be proper under 35 U.S.C. §103, namely, 1) a failure to teach or suggest each and every element of claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35, 37, 38 and 40, and 2) a failure to provide a motivation to produce the claimed methods.

Applicants also respectfully disagree with several statements in the Office Action. For example, at page 7 of the Office Action "applicants has recognized another advantage which would flow naturally *from following the suggestion of the prior art* cannot be the basis for patentability," is inaccurate given that the cited art fails to provide the requisite teaching or suggestion. Again, Wilson *et al.*, Bach, and Tripathy *et al.* alone, or in combination, fail to teach or suggest 1) administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy before formation of inhibitory antibodies, when the gene encodes a protein that is the same species as the mammal; and 2) using animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein in gene therapy protocols.

Likewise, the statement in the Office Action at page 7, that "Wilson or Bach teach that it is advantageous....to co-administer an immunosuppressive agent....with a recombinant virus comprising a therapeutic gene" overstates Wilson *et al.* and Bach because these references only report co-administering an immunosuppressive agent when the gene encodes a protein that is a different species than the animal to which it is delivered, and to animals that do not have a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. There is no teaching or suggestion whatsoever in either Wilson *et al.* or Bach to administer an immunosuppressive agent prior to or simultaneously with gene therapy, where the gene encodes a protein that is the same species as the animal into which the protein is delivered, or to an animal having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Consistent with Applicant's position is that 1) the cited references report an immune response is produced in mice delivered genes encoding proteins from different species; 2) no immune response is produced in mice delivered genes encoding mouse proteins; and 3) no animal having genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein were mentioned, let alone employed . Consequently, in view of the fact that the data in the cited references

indicate that an immune response is produced in mice only when the mice are delivered transgenes encoding proteins from a different species, it cannot objectively be argued that the skilled artisan would have had a motivation to administer an immunosuppressive agent prior to or simultaneously with gene therapy, when the delivered gene encodes a protein that is the same species as the animal, let alone to an animal having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein.

Moreover, because Tripathy *et al.* report that murine EPO delivered to mice by way of gene therapy did NOT induce inhibitory antibodies against the murine EPO, Tripathy *et al.* teach away from administering an immunosuppressive agent prior to or simultaneously with gene therapy, where the delivered protein is the same species as the mammal. Herzog Blood also teach away from the claimed methods because the authors reported that mammals (dogs) administered a gene therapy vector encoding a protein (canine factor IX) that is the same species as the mammal to which it was delivered did not produce inhibitory antibodies against the protein. In view of the fact that both Tripathy *et al.*, and Herzog Blood independently found that delivery of a protein by way of gene therapy, where the delivered protein is the same species as the animal, did not result in production of inhibitory antibodies against the protein, the skilled artisan would not have been motivated to administer an immunosuppressive agent prior to or simultaneously with gene therapy, when the gene encodes a protein that is the same species as the mammal to which it is delivered. Consequently, both Tripathy *et al.* and Herzog Blood teach away from the claimed methods.

Accordingly, it is clear that the Patent Office is reading into the cited references knowledge gleaned from Applicants' specification to reconstruct the invention. However, the courts have consistently held this to be improper. see, for example, *In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1971).

In sum, Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, fail to teach or suggest administering an immunosuppressive agent 1) prior to or simultaneously with gene therapy, prior to the mammal forming inhibitory antibodies against the delivered protein, where the protein delivered by way of gene therapy is the same species as the mammal; or 2) to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Further in view of the fact that none of Wilson *et al.*, Bach or Tripathy *et al.* report that delivering a gene encoding a protein that is the same species

as the animal to which it was delivered elicited inhibitory antibodies against the delivered protein, clearly the skilled artisan would not have had the requisite motivation to produce the claimed methods, at the time of the invention. Finally, given the fact that both Tripathy *et al.* and Herzog Blood report that no inhibitory antibodies are produced against proteins delivered by way of gene therapy, when the proteins are the same species as the animal to which it is delivered, Tripathy *et al.* and Herzog *et al.* each teach away from producing the claimed methods.

In view of the foregoing, that Wilson *et al.*, Bach and Tripathy *et al.* 1) fail to teach or suggest each and every element of the claimed methods; 2) fail to provide the requisite motivation to produce the claimed methods; and that 3) Tripathy *et al.* and Herzog *et al.* teach away from producing the claimed methods, claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35, 37, 38 and 40, would not have been obvious in view of Wilson *et al.*, Bach and Tripathy *et al.* Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) in view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al., Nilsson et al. and Warrier et al.

The rejection of claims 1, 12 to 14, 21, 23 to 25 and 39 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is respectfully traversed. The grounds for rejection are as in the record.

The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* are discussed above. In brief, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the protein delivered by way of gene therapy is the same species as the mammal. Furthermore, because none of Wilson *et al.*, Bach, or Tripathy *et al.* report that inhibitory antibodies are produced against proteins delivered by way of gene therapy to mammals, when the protein is the same species as the mammal, the skilled artisan would not have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against the protein delivered by way of gene therapy that is the

same species as the mammal, at the time of the invention. Moreover, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent as in the claimed methods to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein.

Neither Nilsson *et al.* nor Warrier *et al.* correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* For example, Nilsson *et al.* report studies in which hemophiliacs that produce factor IX antibodies were treated with high doses of IgG with cyclophosphamide and factor IX; however, Nilsson *et al.* fail to teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal to which it is delivered, let alone teach or suggest that an immune response is elicited to a protein delivered by way of gene therapy, when the protein is the same species as the mammal to which is delivered. Furthermore, Nilsson *et al.* fail to teach or suggest treating hemophiliacs prior to formation of inhibitory antibodies, as in the claimed methods. In this regard, all hemophiliacs were treated after they had developed inhibitory antibodies against factor IX, and Nilsson *et al.* is silent regarding treating hemophiliacs prior to forming inhibitory antibodies. Consequently, Nilsson *et al.* fail to correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.*

Moreover, Nilsson *et al.* 1) fail to provide the requisite motivation to produce the claimed methods; and 2) teach away from the claimed methods. In support of Applicant's position, Nilsson *et al.* report that in three patients, "treatment with factor IX and cyclophosphamide was ineffective, resulting in high and persistent anamnestic response." (see page 9173, first sentence under "*Discussion*") The fact that Nilsson *et al.* state that cyclophosphamide combined with factor IX treatment was ineffective would obviously teach the skilled artisan away from administering cyclophosphamide, prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal, let alone that inhibitory antibodies are produced against a protein delivered by way of gene therapy, when the protein is the same species as the mammal to which is delivered. Consequently, the skilled artisan would not have been motivated to produce the claimed methods in view of Nilsson *et al.* which, furthermore, teach away from the claimed methods.

Warrier *et al.* report the presence of factor IX inhibitors in hemophiliacs, which is associated with the total absence of factor IX antigen due to FIX deletions or other major rearrangements; however, as with the four other cited references, Warrier *et al.* fail to teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the protein delivered is the same species as the mammal to which it is delivered, let alone teach or suggest that an immune response is elicited to a protein delivered by way of gene therapy, when the protein is the same species as the mammal to which is delivered. Furthermore, as with Nilsson *et al.*, Warrier *et al.* also fail to teach or suggest treating mammals prior to formation of inhibitory antibodies. Consequently, Warrier *et al.* fail to correct the deficiencies of Wilson *et al.*, Bach, Tripathy *et al.* and Nilsson *et al.*

At most, Warrier *et al.* suggest molecular diagnosis to identify children at greatest risk of severe hemophilia B, recommending that those with frameshift or deletion mutations be "monitored more closely during their first exposure to FIX." (page S127, right column, second full paragraph). However, Warrier *et al.* fail to even mention administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal to which it is delivered, to children so diagnosed. Absent such a teaching or suggestion, Warrier *et al.* fail to provide that which is missing from Wilson *et al.*, Bach, Tripathy *et al.* and Nilsson *et al.*

Furthermore, the fact that Warrier *et al.* discuss several alternative reasons for the development of inhibitors evidences that the authors do not understand why inhibitors form. For example, one hypothesis which the authors state "is an attractive one to consider," is that there is a deletion of neighboring genes that modulate the immune response (page S126, left column, third full paragraph). Because Warrier *et al.* fail to understand why inhibitors develop, Warrier *et al.* cannot objectively be said to teach or suggest to the skilled artisan a particular way to prevent or inhibit formation of the inhibitors. Thus, because Warrier *et al.* cannot fairly be said to teach or suggest to the skilled artisan a particular way to prevent or inhibit formation of inhibitors, surely Warrier *et al.* cannot be said to teach or suggest the specifically claimed methods, let alone provide a motivation or reasonable expectation of success of producing the specifically claimed methods.

Finally, as discussed above and in the record, Tripathy *et al.* and Herzog *et al.* each report that animals delivered two different proteins via gene therapy, where the protein is the same

species as the animal, did not produce inhibitory antibodies against the delivered proteins. In view of the fact that these two independent investigators found that no inhibitory antibodies were produced against proteins delivered by way of gene therapy, where the delivered protein is the same species as the animal to which it is delivered, the skilled artisan at the time of the invention would have had no logical reason to use an immunosuppressive agent prior to or simultaneously with gene therapy, when the gene encodes a protein that is the same species as the mammal to which it is delivered. Again, no immune response was elicited against the protein delivered by way of gene therapy, so there is no logical reason to administer an immunosuppressive agent prior to or simultaneously with gene therapy. Consequently, each of Tripathy *et al.*, and Herzog *et al.* teach the skilled artisan away from producing claims 1, 12 to 14, 21, 23 to 25 and 39.

In view of the foregoing, claims 1, 12 to 14, 21, 23 to 25 and 39 would not have been obvious over Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* alone, or in any combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al. and Herzog et al.

The rejection of claims 1, 3, 6 to 8, 13, 14, 16 and 33 to 36 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997), referred to herein as "Herzog PNAS") is respectfully traversed. The grounds for rejection are as in the record.

Claims 1, 3, 6 to 8, 13, 14, 16 and 33 to 36 would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, and Herzog PNAS alone, or in any combination. The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* have been discussed at length above and in the record. In brief, neither Wilson *et al.*, Bach nor Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, prior to the mammal forming inhibitory antibodies, where the delivered protein is the same species as the mammal to which it is delivered. Thus, Wilson *et al.*,

Bach and Tripathy *et al.* fail to teach or suggest each and every element claimed. Moreover, none of Wilson *et al.*, Bach, nor Tripathy *et al.* report mammals producing inhibitory antibodies against proteins delivered by way of gene therapy, when the protein is the same species as the mammal. Thus, the skilled artisan would not have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against the protein or blood coagulation protein delivered by way of gene therapy that is the same species as the mammal, at the time of the invention. Consequently, Wilson *et al.*, Bach and Tripathy *et al.* fail to teach or suggest each and every element of the claimed methods, as well as fail to provide the requisite motivation to produce the claimed methods.

Herzog PNAS does not correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* In brief, Herzog PNAS reports injection of recombinant adeno-associated virus vector expressing human factor IX in hindlimb of mice, which developed antibodies against the human factor IX. Subsequent studies in which rag 1 mice were injected were reported to produce therapeutic levels of human factor IX in plasma. However, as with all the other five cited references, Herzog PNAS does not teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, prior to formation of inhibitory antibodies, where the protein delivered by way of gene therapy is the same species as the mammal to which it is delivered. Nor does Herzog PNAS teach or suggest that inhibitory antibodies are produced against a protein delivered by way of gene therapy, where the delivered protein is the same species as the mammal to which it is delivered. Finally, Herzog PNAS fails to teach or suggest administering an immunosuppressive agent to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, let alone in the manner claimed. Absent such a teaching or suggestion, Herzog PNAS fails to provide that which is missing from Wilson *et al.*, Bach and Tripathy *et al.* and, furthermore, fails to provide the skilled artisan with a motivation to administer an immunosuppressive agent to a mammal or human prior to or simultaneously with gene therapy, when the protein or blood coagulation protein delivered by way of gene therapy is the same species as the mammal to which it is delivered, and the mammal or human has a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein.

Further in view of the fact that Tripathy *et al.* and Herzog Blood teach that no inhibitory antibodies are produced in mammals delivered proteins by way of gene therapy, where the delivered proteins are the same species as the animal to which it is delivered, the skilled artisan would not be motivated to administer an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, when delivered protein is the same species as the animal to which it is delivered. Consequently, both Tripathy *et al.* and Herzog Blood teach away from producing the claimed methods.

In view of the foregoing, claims 1, 3, 6 to 8, 13, 14, 16 and 33 to 36 would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, or Herzog *et al.* alone, or in any combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997)) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4, 6 to 10, 12 to 21, 23 to 25, 28, 29 and 31 to 40 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

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